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EXPERIMENTAL HYPERTENSION INDUCED BY RENAL ISCHEMIA

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ALTHOUGH the direct method for the determination of blood pressure in animals dates back to Stephen Hales,[1] in 1733, and although the existence of a state of increased vascular tension in man was surmised on the basis of indirect methods, especially palpation of the pulse,[2] pulse tracings[3-5] and other bloodless indirect methods,[6-8] yet it was not until the development by Riva-Rocci[9] of the method of taking blood pressure (actually bursting tension) by the pneumatic cuff and mercury manometer that the existence and significance of human hypertension were fully recognized and the serious study of its cause was undertaken.

Whether or not disease of the kidneys plays a primary part in the pathogenesis of increased arterial tension has been the subject of speculation and controversy for a long time. More than 100 years ago, before blood pressure had been determined in man, Richard Bright[10,11] observed the frequent coexistence of renal disease of various kinds and hypertrophy

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of the heart for which he found no obvious cause in the heart or large blood vessels. He attributed the cardiac hypertrophy to an effect produced on the heart (increased action) or blood vessels (increased peripheral resistance) by an altered state of the blood which, he felt convinced, was caused by the renal disease, although he admitted the possibility that the renal disease might be the result of the altered state of the blood. Thus, although Bright knew nothing about hypertension, we now realize that he was the first to consider the possible renal origin of this condition. He tried to perfuse nodular kidneys and mentioned the resistance which the nodules offered to injection. Toynbee[12] found that this difficulty was due to thickening of wall and narrowing of lumen of the smaller intrarenal arteries. This has since been fully confirmed by direct[13-16] and indirect[17-19] methods. Johnson[20] showed that in such cases similar thickening in the small arteries was present in other organs; yet he offered the theory that the primary disease was within the kidney, and that cardiac hypertrophy and increased arterial tension were due to generalized constriction of the peripheral branches of the arterial system. For the vasoconstriction he had a far-fetched teleological explanation to the effect that the vascular disease would interfere with the passage of accumulated noxious substances from the blood into the tissues. Traube[2] was the first to express the definite view of a primary causative relationship between renal disease and increased arterial tension. This was based on the mechanical theory of the resistance which the disease in the kidneys offers to the loss of water from the blood and also to the amount of blood leaving the aorta, with consequent hydremia and increased arterial tension. This view has not been substantiated by subsequent authors except those who have used his theory as a basis for a teleological explanation of hypertension. It was principally as a result of the anatomical studies of Gull and Sutton,[21] who demonstrated the rather widespread distribution of organic disease of the smallest branches of arteries and the capillaries, which they called arteriocapillary fibrosis, that these generalized organic changes were seriously considered as the primary cause of increased peripheral resistance, with consequent hypertension and cardiac hypertrophy. The clear differentiation of chronic glomerulonephritis and renal arteriolar sclerosis[22,23] finally led to the recognition of Frank's[24] essential hypertension. The hypertension associated with chronic glomerulonephritis was quite generally regarded as renal in origin so that the problem became limited to the pathogenesis

of essential hypertension. To the followers[25,26] of Gull and Sutton, the cause of the hypertension appeared to have been explained, but there remained the problem of the cause of the primary vascular disease. The pendulum swung when it was realized that the organic disease of the arterioles, even in the most severe cases, was not sufficiently widespread to account for the increased peripheral resistance that is required to cause persistent hypertension. Huchard[27] and Allbutt[28] projected the idea that the hypertension, due to generalized vasoconstriction, is the primary manifestation and the organic vascular disease a consequence of this condition. Mueller[29] went so far as to assert that prolonged vasoconstriction in a localized zone, such as the splanchnic, could be the cause of essential hypertension. The problem then became one of finding the cause of such generalized or localized vasoconstriction, with the kidney not seriously considered as the primary source of this effect. Both groups considered the vascular disease of the kidney simply a part of the generalized disease process and did not assign to it a primary part in the origin of this type of hypertension.

It is now generally accepted that hypertension may be of renal origin but this is usually assigned to the hypertension that accompanies obstructive disease of the urinary passages, chronic glomerulonephritis, polycystic kidney, renal panarteritis and severe renal amyloidosis.[30] Yet there are those, like Kylin,[31,32] who go so far as to deny the renal origin of hypertension under all conditions and who regard the various types of renal disease accompanying hypertension as secondary or merely coincidental. Fishberg[30] has defined essential hypertension as persistently elevated blood pressure without known cause which, on neither clinical nor anatomical grounds, can be considered due to inflammatory or obstructive renal disease. Although Fishberg includes various types of hypertension in this category, yet by far the commonest is the type associated with so-called diffuse vascular disease. Most of the recent writers[36-40] on the subject have assigned this term to this condition and agree with Fishberg that it is not of renal origin. The usual arguments against the renal origin of essential hypertension have been: (a) the frequent discovery of elevated blood pressure before there are any recognizable signs of impairment of renal function;[42] (b) the fact that in a large percentage of these cases renal insufficiency never does become manifest; and (c) the failure to find any anatomical signs of renal disease in some of these cases. Fishberg,[33] Bell and Clawson,[34] and Moritz

and Oldt[35] have found that at autopsy there is organic arteriolar disease in the kidneys of most individuals who have had essential hypertension, without signs of renal functional damage during life. Yet only Moritz and Oldt,[35] the most recent investigators of this phase, have drawn the conclusion from their results that the vascular disease of the kidney must be seriously considered as playing a primary part in the pathogenesis of essential hypertension. In the reports of cases of essential hypertension in which no intrarenal arteriolar disease was found,[30] the possibility was not usually excluded that severe sclerosis in some portion of the main renal arteries might have been the cause of renal ischemia. During the past year, in a few cases of hypertension without renal arteriosclerosis, severe sclerosis and narrowing of the orifice or lumen of the main renal arteries or the lumen of the larger extrarenal branches, obviously sufficient to cause renal ischemia, have been observed.[41] Formerly lesions of this kind have probably been overlooked and the cases classified as essential hypertension without renal vascular disease.

Experimental evidence or proof for the view that the kidney may play a primary part in the development of hypertension has been sought in a variety of ways that appear in the following summary:

A SUMMARY OF OTHER EXPERIMENTS DESIGNED TO DETERMINE THE POSSIBLE RENAL ORIGIN OF HYPERTENSION

Bilateral nephrectomy.

Mosler[43] (1912). Used rabbits. Insignificant elevation of blood pressure.
Backmann[44] (1916). Used cats. No elevation of blood pressure.
Cash[45] (1926). Used dogs. No elevation of blood pressure.
Hartwich[46,47] (1930). Used dogs. No elevation of blood pressure.
Harrison, Blalock and Mason[139] (1929, 1936). Used dogs. No elevation of blood pressure in 16 out of 18 dogs.

Reduction of the amount of functioning renal tissue.

Grawitz and Israel[49] (1879). Used rabbits. Slight hypertrophy of heart, interpreted by the authors as due to hypertension.
Pässler and Heineke[50] (1905). Used dogs. Slight elevation of blood pressure.
Backmann[44] (1916). Used cats. Slight elevation of blood pressure.
Allen and collaborators[51] (1925). Used dogs. Slight temporary elevation of blood pressure.
Mark[52a,b] (1925, 1928). Used dogs. Slight elevation of blood pressure.
Anderson[54] (1926). Used rabbits. No elevation of blood pressure.
Hartwich[46,47] (1929, 1930). Used dogs. No elevation of blood pressure.
Friedmann and Wachsmuth[55] (1930). Used dogs. No elevation of blood pressure.
Chanutin and Ferris[56] (1932). Used rats. Great elevation of blood pressure.
Wood and Ethridge[86] (1933). Used rats. Hypertension.
Rytand and Dock[57] (1935). Used rats. Great elevation of blood pressure.

Reduction of amount of renal substance by coagulation necrosis due to ligation of branches of renal arteries.

Janeway[58,59] (1908, 1913), assisted by Carrel[53] (1909). Used dogs. Slight elevation of blood pressure.

Mark[52b] (1928). Used dogs. No elevation of blood pressure.

Hartwich[46,47] (1929, 1930). Moderate elevation of blood pressure. Not persistent.

Friedmann and Wachsmuth[55] (1930). Moderate elevation of blood pressure. Not persistent.

Reduction of amount of renal substance by partial renal excision and unilateral nephrectomy combined with coagulation necrosis of part of the remaining kidney by ligation of branches of renal artery.

Cash[60] (1924). Used dogs. Slight to moderate temporary elevation of blood pressure.

Hantschmann[69] (1931). Used dogs. Slight elevation. Not persistent.

Mark and Giesendörfer[61] (1930). Used dogs. Moderate temporary elevation of blood pressure.

Ferris and Hynes[62] (1931). Used dogs. Slight temporary elevation of blood pressure.

Destruction of renal substance by irradiation of kidneys with roentgen rays.

Hartman, Bolliger and Doub[63] (1926). Used dogs. Moderate elevation of blood pressure.

Page[89] (1935). Used dogs. Moderate elevation of blood pressure.

Renal infarction due to multiple emboli.

Senator[65] (1911). Used cats. Injected liquid paraffin into renal arteries. No rise of blood pressure.

Cash[60] (1924). Used dogs. Injected insoluble Berlin blue. No elevation of blood pressure.

Apfelbach and Jensen[66] (1931). Used dogs. Injected particles of charcoal into renal arteries. No elevation of blood pressure.

Occlusion of one main renal artery.

Hartwich[46,47] (1929, 1930). Used dogs. Slight temporary elevation of blood pressure.

Friedmann and Wachsmuth[55] (1930). Used dogs. Slight temporary elevation of blood pressure.

Occlusion of both main renal arteries.

Katzenstein[67] (1905). Used rabbits and dogs. No rise of blood pressure.

Cash[45] (1926). Used dogs. Moderate to severe elevation of blood pressure.

Occlusion (permanent or intermittent) of renal arteries, veins and ureters.

Cash[45] (1926). Permanent occlusion. Used dogs. No elevation of blood pressure.

Loesch[68] (1933). Intermittent brief occlusion, every two or three days. Used dogs. Moderate persistent elevation of blood pressure.

Partial constriction of renal arteries (acute experiments).

Katzenstein[67] (1905). Used dogs. Very slight elevation of blood pressure.

Bridgman, E. W. and Hirose, K.[74] (1918). Used dogs. No elevation of blood pressure.

Passive hyperemia (constriction of renal vein) of one kidney.

Pedersen[64] (1927) and Bell and Pedersen[70] (1930). Used dogs. Moderate temporary elevation of blood pressure.

Menendez[71] (1933). Used dogs. Slight temporary elevation of blood pressure in some; none in others.

Compression of kidneys by oncometer.

Alwens[72] (1909). Used cats. Acute experiments. Slight elevation of blood pressure.

Permanent obstruction of ureters.

Hartwich[46,47] (1929, 1930). Used dogs. Moderate elevation of blood pressure.

Harrison, Mason, Resnik and Rainey[73] (1936). Used dogs. Moderate elevation of blood pressure.

Temporary obstruction of one ureter followed by release of obstruction and excision of other kidney.

Rautenberg[75] (1910). Used rabbits. Moderate elevation of blood pressure.

Effect of nephrotoxic substances.

Dominguez[76] (1928). Used rabbits. Injected uranium salts. No elevation of blood pressure except in one animal that developed severe arterial and arteriolar sclerosis, especially in the kidneys.

Arnott and Kellar[77,78] (1935, 1936). Used rabbits. Injected sodium oxalate. Moderate temporary elevation of blood pressure.

Scarff and McGeorge[79] (1937). Used rabbits. Injected sodium oxalate. No elevation of blood pressure.

In some of the earlier investigations mentioned in the summary the hypertension that was observed was usually slight and lasted from only a few hours to several days. Some of the later investigators reported the development of hypertension of moderate degree and of short duration while others succeeded in producing moderate or severe hypertension of longer duration. Under practically every heading contradictory reports occur. Some of these experiments merely proved what is generally accepted, even for man, namely, the renal origin of hypertension associated with obstruction of the urinary passages or great destruction of renal parenchyma.[30] The contradictory results obtained by different investigators were due partly to the various methods, some indirect, like cardiac hypertrophy, which were used for determining the existence of hypertension, the different types of animal employed and the slight changes of blood pressure which were regarded as significant by some and not by others. For some of the contradictory results[77,78,79] there is no obvious explanation. The results of the experiments performed up to

1928 did indicate that various pathological changes in the kidneys could in some way play a primary part in initiating a degree of at least temporary hypertension in animals. By none of these methods was the condition produced in the kidneys comparable to that of the kidneys in human essential hypertension associated with arteriolar disease. It would appear that those experiments that were designed to prove the renal origin of essential hypertension failed for several reasons: 1. They were acute experiments and yielded negative or contradictory results in the hands of different investigators using the same methods. 2. In most of the chronic experiments, the experimental conditions did not reproduce or even simulate the anatomical or functional state of the kidneys in benign essential hypertension. 3. Hypertension, when produced, did not persist. Any method for the experimental determination of the possible primary part played by renal arteriosclerosis in the origin of essential hypertension should involve the production of at least the physiological effect of the renal vascular disease. It is not actually known, but it is at least probable, that the effect is a decrease of the flow of blood to the functioning elements of the kidney and a decrease in the intraglomerular capillary pressure. The latter would not be correct if the view is valid that there is spasm of the efferent arterioles[80] or the capillaries[81] of the glomeruli in essential hypertension.

Up to 1928, when the experimental investigations of the author were begun, no one had succeeded in producing either generalized arteriolar sclerosis or arteriolar sclerosis limited to the kidneys. For these investigations, therefore, the following working hypothesis was adopted: If organic disease of the kidney be the initiating factor in the pathogenesis of benign essential hypertension, then this disease is, in all probability, the arteriolar sclerosis which is so frequently associated with this condition. If arteriolar sclerosis limited to the kidneys can be the primary factor in initiating this type of hypertension, then the necessary conditions for the establishment of the renal origin of essential hypertension upon an experimental basis should be the production of hypertension in animals by any method which will produce at least the physiological effects of such renal vascular disease. Since there is no known way of producing arteriolar sclerosis localized to the kidney, it was thought that the effects of arteriolar disease could probably be produced by constricting the main renal arteries. Katzenstein,[67] and Bridgman and Hirose[74] did try to produce hypertension by constricting the main renal arteries, but the experi-

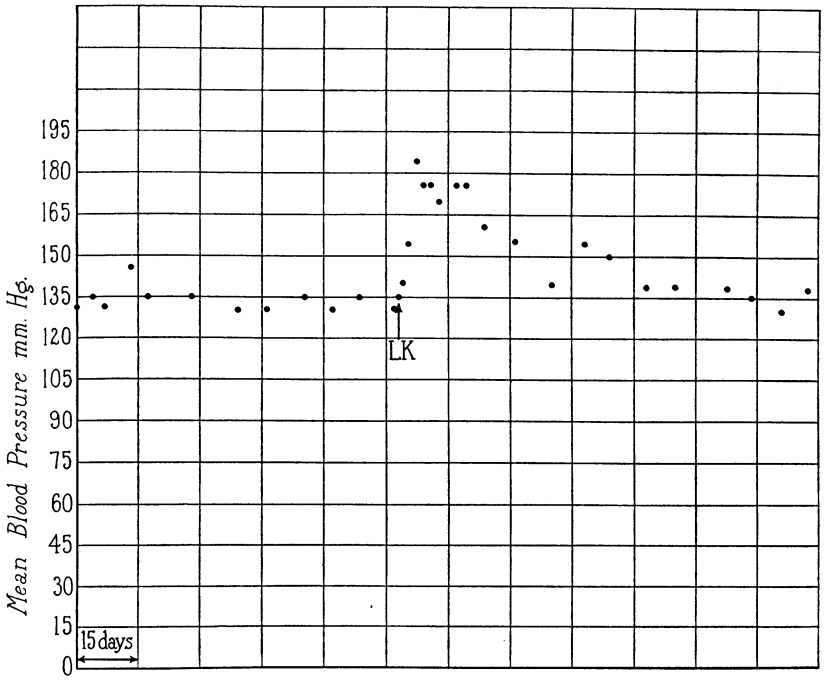

Fig. 1—Dog-3-35, male, chow, young. Initial weight 12.4 kg. Final weight 14.0 kg. LK = left main renal artery—moderately constricted. ● = Mean blood pressure, mm. Hg, direct method, femoral artery.

ments were very short and their results contradictory. Bridgman and Hirose observed no elevation and Katzenstein a very slight rise (10 mm. Hg.) of mean blood pressure. For the purpose of the author's experiments, a special type of silver clamp was devised[83] whereby the main renal arteries could be constricted and their lumina reduced to any desired caliber. It was first demonstrated[83] that decrease of the lumen of the main renal artery by varying degrees of compression caused an immediate corresponding decrease of blood flow through the kidney. Whether the decreased blood flow persists after hypertension develops has not yet been determined. A decrease of intraglomerular capillary pressure as a result of this procedure has been assumed but not proved.

In a series of experiments, by the use of this method, it has been found that, in the dog[82,83,84] and monkey,[85] constriction of the main artery of one kidney results in elevation of blood pressure which persists from weeks to months but usually returns to a lower or to the original level within one month (Fig. 1). The adequate constriction of both

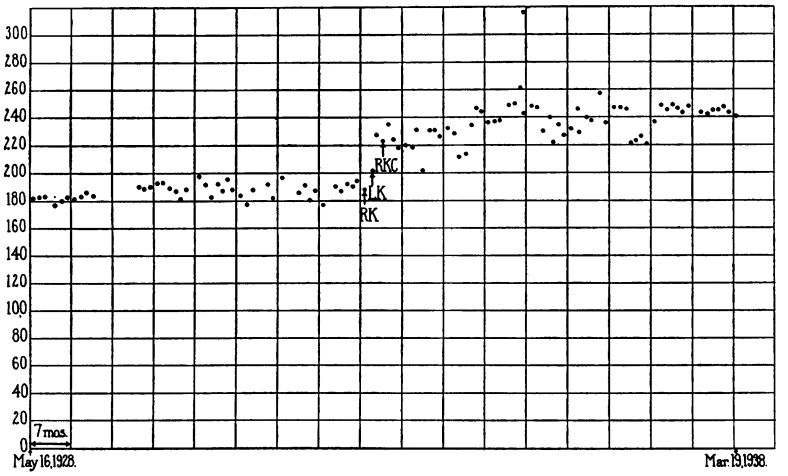

Fig. 2—"Blackie", short-haired mongrel, female, age about 1 year, in 1928. Initial weight 21.4 kg. Present weight 21.6 kg. RK = moderate constriction of right main renal artery. LK = moderate constriction of left main renal artery. RKC = occlusion of right main renal artery. The animal is still alive. ● = Systolic blood pressure, mm. Hg, van Leersum carotid loop method.

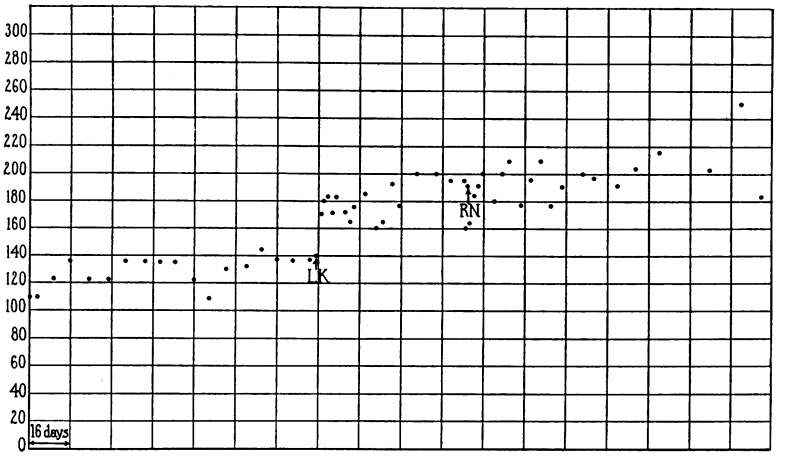

Fig. 3—Dog 3-14, male, bull-dog, young. Initial weight 11 kg. Present weight 11.8 kg. LK = severe constriction of left main renal artery. RN = right nephrectomy. ● = Mean blood pressure, mm. Hg, direct method, femoral artery.

main renal arteries at the same time, or with an interval between the clampings, results in persistent hypertension (Fig. 2). The same persistent effect on blood pressure has been obtained by first constricting the main artery of one kidney and later removing the other kidney (Fig. 3). In

some animals with both renal arteries constricted, the elevated blood pressure also tends after a while to return to a lower level. This is probably due to the development of significant accessory circulation to the kidney, which is naturally abundant in the dog.[210] In such dogs, increasing the constriction of the main renal arteries usually results in re-elevation of blood pressure. In some dogs, collateral circulation has become so well established that one or both main renal arteries have been finally entirely occluded and such animals have survived several years with greatly elevated blood pressure without accompanying significant impairment of renal function. It has been shown that the hypertension which has been produced by these methods in dogs and monkeys involves elevation of both diastolic and systolic pressure.[84,85,91] A similar effect in the upper part of the body can be obtained by constricting the aorta immediately above the origin of both main renal arteries.[87] Indirect confirmation of this is the development of left ventricular hypertrophy in the rat after constriction of the aorta immediately above the origin of the renal arteries.[225] Contriction of femoral or splenic arteries,[46,47,48,83] of splanchnic arteries,[213] or the aorta immediately below the origin of both renal arteries[87] does not elevate blood pressure. Most of these results have now been fully confirmed and amplified by many investigators.[89-92,97,214]

When the constriction of both main renal arteries, the main artery of the only kidney, or the aorta above the origin of the renal arteries is made moderate, there is no accompanying disturbance of renal function, detectable by the usual studies of urine and blood, including urea and creatinine clearance tests.[83,84,85] In some of the animals, with the main renal arteries constricted, the hypertension has persisted at a very high level for more than five years (Fig. 2). In the animals with the aorta constricted above the origin of both main renal arteries there has been a much greater tendency to return to the original level. In these, in order to make the hypertension persist, it has been found necessary also to constrict the aorta below the renal arteries. Despite this additional procedure, the accessory circulation to the kidney appears to be adequate to interfere with persistence of the hypertension at a high level.[87] In those animals that have had long standing hypertension, without accompanying damage of renal function, the only significant changes in the vascular system observed so far have been degenerative changes, mainly intimal, in the arterioles of the retina[93] and thickening of the media of the arterioles

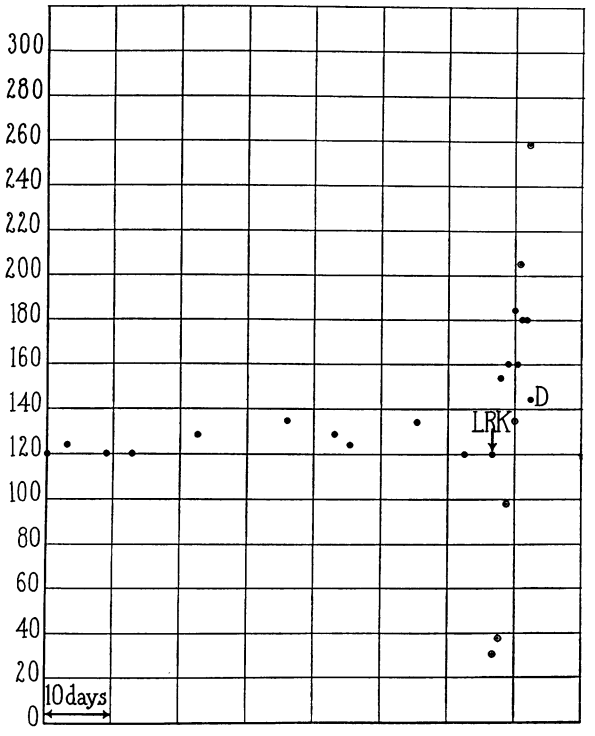

Fig. 4—Dog 3-90, female, mixture of collie and airdale, middle-aged. Initial weight 10.9 kg., final weight 12.2 kg. LRK = almost complete constriction of left and right main renal arteries. D = died. ● = Mean blood pressure, mm. Hg, direct method, femoral artery. ⊙ = Blood urea nitrogen, mg. per 100 cc. of plasma.

in other organs, especially skeletal muscle. The changes in the kidneys affect mainly the tubules. The organ may show but little change[99] or may undergo atrophy, depending upon the severity of the constriction.[83,84] In such animals hypertrophy of the heart has been reported.[92,99]

If the constriction of the renal arteries or of the aorta is made severe or complete from the beginning, disturbance of renal function usually accompanies the elevated blood pressure and the animal may develop fatal uremia.[83,84,85] In some of these animals (Fig. 4) there develop widespread fibrinoid and hyaline degeneration, and necrosis of arterioles, with petechiae in some organs, similar in all respects to the lesions observed in the acute malignant phase of essential hypertension in man (see Plate).

The mechanism of development of the benign phase of experimental

hypertension induced by renal ischemia has now been the subject of extensive investigation. In considering the pathogenesis of this type of hypertension it has been assumed, for the same reasons as for human essential hypertension,[30,94] that the responsible mechanism is increased peripheral resistance. Since, in the experimental animals, this cannot be regarded as due to initial organic change in the peripheral portion of the entire vascular system, the problem narrows down to the cause of the functional increase of peripheral resistance which follows the constriction of the main renal arteries. The teleological explanation[208] of purposeful increase of peripheral resistance in order to elevate the pressure and improve the blood flow through the ischemic kidneys is not susceptible to proof. There are, therefore, but two known mechanisms whereby the generalized constriction of arterioles[30] and increased peripheral resistance can be produced; namely, either a nervous reflex from the ischemic kidneys, which affects the general vasomotor apparatus, or a humoral mechanism initiated by the ischemic kidneys due to the formation or accumulation in the blood of a substance which, directly or indirectly, constricts the peripheral vessels. The possibility that such a substance might act on capillaries[96] or by neutralizing a natural depressor substance must also be mentioned.

That the ischemic kidneys are in some way directly responsible for the development of the experimental hypertension has been shown by

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*EXPLANATION OF PLATE**

This Colored Plate Represents a Photomicrograph in color Prepared by the Separation Method.

Fig. 1—Arteriole in submucosa of large intestine. Beginning subendothelial deposit of hyalin. Endothelium well preserved. Hematoxylin and eosin. ×265.

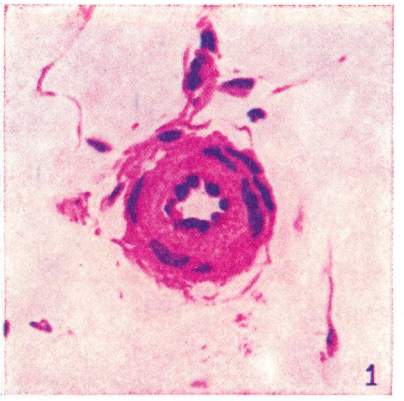
Fig. 2—Arteriole in submucosa of stomach. Obliterative hyalinization of intima, endothelium still recognizable but nuclei reduced in number and pyknotic. Hematoxylin and eosin. ×430.

Fig. 3—Arteriole in submucosa of small intestine. Lumen completely obliterated by accumulation of hyalin containing a few pyknotic nuclei. Hematoxylin and eosin. ×430.

Fig. 4—Arteriole in submucosa of stomach. Portion of entire thickness of wall necrotic. Normal thickness of wall and lumen natural size. Hematoxylin and eosin. ×325.

Fig. 5—Arteriole, cut longitudinally, in submucosa and mucosa of large intestine. Partly hyalinized, partly necrotic, with extravasated blood around it. A portion of the same arteriole, in the submucosa, immediately proximal to the part included in this figure, was entirely normal. Hematoxylin and eosin. ×255.

* This colored plate reprinted from the *Journal of Experimental Medicine*. Vol. 67, No. 5, 1938.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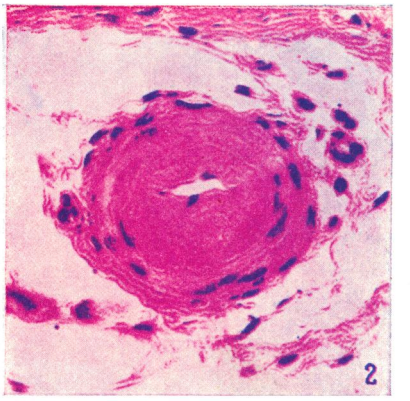
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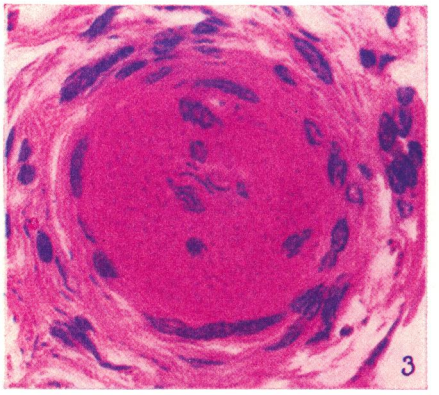
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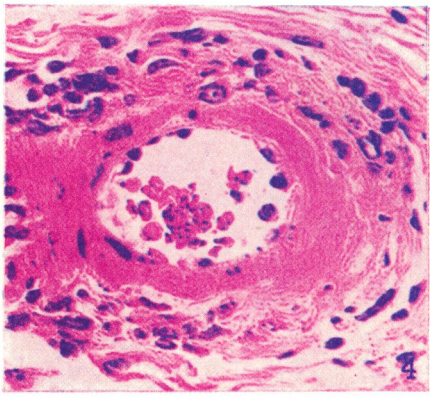
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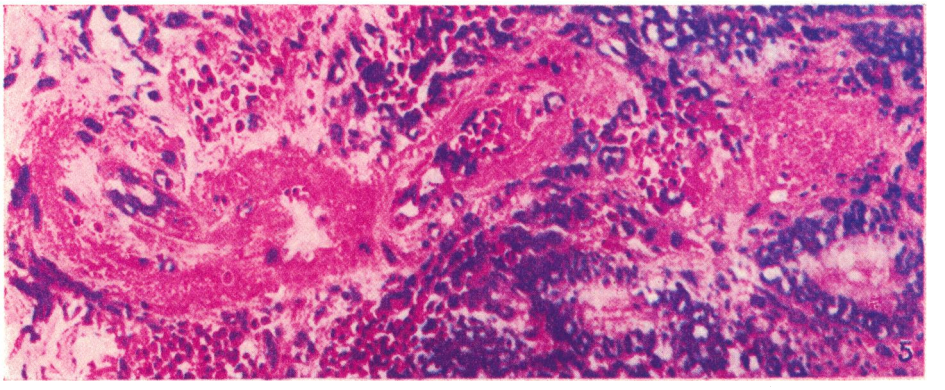
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the following experiments. If the main renal artery of one kidney is constricted and the ischemic kidney is removed some time later, when the blood pressure is still well elevated, the blood pressure falls promptly to the normal level.[84] If, instead of nephrectomy, the clamp on the one ischemic kidney is released or removed, the blood pressure also returns promptly to the original level.[84] If the elevated blood pressure is first produced by the constriction of the main renal arteries of both kidneys, and only one clamp is released, the blood pressure falls slowly to the lower or to the original level in about the same time that it does when only one clamp is applied.[84] If, in a hypertensive animal, both clamps are released, the blood pressure falls promptly to the original normal level.[84] If one kidney is transplanted to the neck or inguinal region and the other kidney removed, constriction of the arterial blood supply to the transplanted kidney results in the development of elevated blood pressure.[97,98] Bilateral nephrectomy is not followed by the development of persistent hypertension.[43-48,84] These results constitute evidence that the kidney is responsible for the effect and that it must be present in the body in order for the hypertension to occur.

The experiments that have been directed toward the study of the possible part played by a nervous reflex from the kidney have failed to establish this as the mechanism responsible for the increased peripheral resistance. In dogs, denervation of the renal pedicle[89,92,99] does not prevent or reduce hypertension due to constriction of the main renal arteries. This differentiates this type of hypertension from that due to intracisternal injection of kaolin[105] which can be prevented or reduced to normal by renal denervation. In the case of hypertension due to denervation of the carotid sinus and section of the depressor nerves the results of investigations of the effect of renal denervation have been contradictory.[108] Section of splanchnic nerves and excision of the lower four thoracic sympathetic ganglia,[100] section of the anterior nerve roots from the sixth dorsal to the second lumbar inclusive,[101] excision of the entire sympathetic nervous system in thorax and abdomen, including cardiac denervation,[102-104] and even pithing,[98] have failed to prevent, or permanently to reduce hypertension produced by constriction of the main renal arteries. Finally, as mentioned above, if one kidney is removed and the other kidney is transplanted to the neck or to the inguinal region, and its main renal artery is constricted, elevated blood pressure develops.[97,98] In such an animal there is no possible direct connection between

kidney and nervous system. The results of these studies eliminate a nervous reflex from the ischemic kidneys as the responsible mechanism for the initiation of the hypertension and leave only a humoral mechanism as the probable explanation of the phenomenon. These experiments do not eliminate the possibility that in human essential hypertension stimuli from the central nervous system may sometimes play a primary part and often an accessory part in elevating blood pressure above the level determined by the renal mechanism. It is probably the nervous factor which is influenced by the usual medical treatment of hypertension and accounts for any fall of blood pressure which results.

The failure of the various surgical procedures carried out on the nervous system to affect experimental hypertension due to constriction of the main renal arteries is probably due to the persistence of the effect on the kidney which cannot be materially altered by these procedures as long as the clamp remains applied. These experiments do not in any way controvert the results that have been obtained by the same procedures in the surgical treatment of hypertension in man.[112-125,188] They do emphasize, however, the importance of the renal factor as the primary cause of this type of experimental hypertension and probably of human essential hypertension that is associated with renal arteriolar disease. Since the renal factor in man is frequently due to narrowing of the lumen of only the arterioles of the kidney, without narrowing of the lumen of the large arteries, improvement of the circulation might result from the various surgical operations on the nervous system, as a result of relaxation of those arterioles in which the organic changes are not fixed. The lowering of blood pressure reported in about the same percentage of cases of hypertension by surgeons using various procedures which, directly or indirectly, affect the vasomotor nervous mechanism in the abdomen may, therefore, be due mainly to one cause; namely, the improvement of the circulation through the kidneys, and not, as has been suggested, directly to the relaxation of the arterioles in a large part of the vascular bed of the abdomen, independently of any effect on the kidneys. The latter view has no support in experimental observations.

All of the investigations that have been directed toward the study of the pathogenesis of this type of experimental hypertension have yielded results that indicate the existence of a humoral mechanism of renal origin that is responsible for the vascular constriction and consequent increased peripheral resistance which produces the elevation of the blood pressure.

Removal of both kidneys does not result in elevated blood pressure, although the animal develops severe azotemia.[43-48,84] On the contrary, sudden occlusion of the main renal artery of both kidneys, which also results in fatal uremia, does produce hypertension.[45,84] Since occlusion of both main renal arteries does not eliminate all circulation to the dog's kidneys,[210] a chemical substance might still be washed from the kidney into the general circulation. That this is most probably the case is shown by the failure of hypertension to develop when both main renal veins are occluded at the same time that the main renal arteries are constricted or occluded.[84] This is due, presumably, to interference with the entrance of the hypothetical chemical substance into the blood stream. If the ischemic kidney from one animal is transplanted to the neck of a nephrectomized animal, the blood pressure of the latter rises almost immediately after the circulation through the ischemic kidney is restored, while the transplantation of a normal kidney has no effect on the blood pressure.[126,127] This has been interpreted as an indication that some chemical present in considerable concentration in the ischemic kidney, suddenly washed into the circulation of the recipient animal, produces an almost immediate pressor effect. Whether such a "hypothetical effective substance"[84] actually exists and what its nature is has not yet been elucidated. The normal kidney does not acquire this pressor substance in the short period during which it is without circulation before the transplantation is completed.[126,127]

Since the original investigation by Tigerstedt and Bergmann,[128] who obtained a pressor effect with saline extract of normal rabbits' kidneys, when they injected it intravenously into other rabbits, many workers have repeated the experiments with different kinds of extracts, expressed juices and autolysates of normal kidneys of various animals, with conflicting results. Some[129,130] confirmed Tigerstedt and Bergmann's finding; others[131-133] obtained only depressor effects; while most investigators[134-138] found both a depressor and pressor effect, the latter usually following the former. Pressor effects have also been obtained with extracts from other organs.[142] The search for the possible chemical substance involved in the humoral mechanism of renal origin in the cause of experimental hypertension due to constriction of renal arteries has resulted in a number of investigations that have dealt with the presence of a pressor principle in normal and ischemic kidneys. Tigerstedt and Bergmann actually suggested[128] that there might be an increase

of the pressor substance, *rennin* they called it, in the kidneys of hypertensives. The recent isolation by Landis and collaborators[224] of an extract of normal kidney which elevates blood pressure without diminishing skin temperature and without reducing the amplitude of arterial pulsation is of special interest. A similar extract of ischemic kidney should be made and compared quantitatively with the extract of normal kidney.

Several investigators[139,140,211] have reported a larger amount of pressor substance in the watery extract of ischemic kidneys of experimental hypertension due to constriction of main renal arteries and of the arteriosclerotic kidneys of human hypertension as compared with that of normal kidneys. This does not constitute proof that this is the pressor principle involved in the production of hypertension which follows constriction of the main renal arteries or in essential hypertension in man.

Attempts to demonstrate a direct pressor substance in the systemic or renal venous blood or extract of the plasma of animals with experimental hypertension due to constriction of the main renal arteries have failed.[143] This differs from the result obtained with blood from animals with experimental hypertension due to the intracisternal injection of kaolin.[209] The results of tests made on the blood in human essential hypertension, both benign and malignant, have been contradictory; some obtained pressor effects[144-172] and others did not;[173-184] and the transfusion of blood in large quantity from a hypertensive individual to one with normal blood pressure had no effect on the blood pressure of the latter.[185] The pitfalls of investigations of this kind have been emphasized by O'Connor.[186] Thus there is no conclusive proof of the existence of a known or new pressor substance in the blood, spinal fluid, or urine in human essential hypertension, although it has been possible to obtain a pressor effect with blood from cases of paroxysmal hypertension associated with pheochromocytoma.[226]

The possible part played by the endocrine organs in the humoral mechanism of experimental hypertension due to renal ischemia has been the subject of investigation. Page and Sweet[187] have obtained contradictory results on the influence of hypophysectomy on this type of hypertension. Whereas the removal of the hypophysis had little or no influence in preventing this type of hypertension, yet hypophysectomy in hypertensive dogs was followed by a fall of blood pressure to a lower or normal level in some of the animals. The latter result may have been due to the development of adequate accessory circulation to the kidney

and may not have been due to the effect of hypophysectomy. This investigation requires repetition.

The influence of the adrenals has also been studied.[84] The possibility of keeping bilaterally adrenalectomized dogs alive by means of substitution and supportive therapy[189-193] has permitted the performance of a series of experiments on the effect of constricting the main renal arteries of such animals. Briefly, the results have shown that bilateral adrenalectomy without supportive or substitution therapy prevents the development of hypertension due to renal ischemia and causes previously produced hypertension to fall promptly to the normal or to a subnormal level. The result is the same even when supportive treatment in the form of sodium chloride and sodium bicarbonate or sodium citrate is given to the adrenalectomized animals. However, when presumptive substitution therapy in the form of cortical extract, as well as supportive treatment, is given, some of the animals do develop elevated blood pressure despite the absence of both adrenals. That it is the cortex and not the medulla of the adrenals that is important in this connection is shown by experiments in which one adrenal was completely removed, the medulla of the remaining adrenal destroyed, and the entire cortex[83] or only a small portion of it[84] left just sufficient to maintain life. In such animals, the blood pressure became elevated in the usual way when the main renal arteries were constricted. The results of many of the above experiments have already been confirmed[97] and Rogoff and collaborators[227] have shown recently that there is no increase of epinephrine secretion in this type of experimental hypertension. Just how the cortical hormone acts is not elucidated by these experiments. It may act only by playing its usual part in the physiological mechanisms and by insuring a normal state of the blood vessels of the animal. It may produce its effect by sensitizing the blood vessels to the action of the hypothetical effective substance of renal origin, or the reverse. The two substances may act synergistically. These are points that remain to be clarified. What these experiments do indicate is the futility of surgical[194-200,227] or other procedures designed to cure or lower hypertension in man by removal of one or destruction of portions of both adrenals, except in cases of paroxysmal hypertension associated with tumor of the adrenals.[201-207,226]

Nothing is known about the pathogenesis of the arteriolar degeneration and necrosis which are found in many internal organs, but most

frequently in the kidneys[30] and gastrointestinal tract,[35] in human benign or malignant hypertension. The degenerative and necrotizing arteriolar lesions of the animals which have been described above are not distinguishable from those found in most cases of malignant hypertension in man[35] except that they are more severe and more widespread than in the latter. This indicates a greater susceptibility of the dog's arterioles to these changes. In human malignant hypertension, skeletal muscles and lungs also rarely show necrosis of arterioles, although hyalinization and other changes may occur in those of the muscles.[216] The only striking difference between the lesions in man and dog is that in the latter the kidneys do not, while in the former they very frequently do show arteriolar necrosis. This discrepancy is easily explained and actually affords a clue to the pathogenesis of this lesion. In the animals, the intravascular pressure, within the kidney, is low, because the ischemia is due to the constriction of the main renal artery. In man, the intrarenal vascular tension is undoubtedly high, because there is sclerosis and constriction of the preglomerular arterioles. In some of the larger vessels of the human kidney the lumen is also frequently narrowed, due to proliferation of the intima, but it has never been shown that the arterioles belonging to such vessels become necrotic. It may be that only those arterioles become necrotic that are subjected to the high bursting tension as well as to the hypothetical toxic substance or substances in the blood which result from the renal insufficiency. There are some human cases in which necrosis of small renal arterioles is not found. These may be cases in which the renal insufficiency is due to widespread intimal proliferation in the small arteries and large arterioles and not to the reduction in the caliber of the preglomerular arterioles. This may also account for the difference and point to one of the probable factors and necessary conditions in the pathogenesis of arteriolar necrosis and hemorrhage; namely, elevated pressure within these vessels. That the accumulation of chemicals in the blood is not by itself a sufficient condition for the production of the arteriolar lesions, is shown by the fact that bilaterally nephrectomized dogs that develop azotemia but no hypertension[84] do not develop the generalized hyalinization and necrosis of arterioles and associated hemorrhages in the organs. That hypertension alone is not sufficient to determine the formation of the necrotizing lesions of the arterioles is shown by the fact that animals that have had severe hypertension for more than five years, without accompanying significant

disturbance of renal excretory function, have not developed this lesion. That the lesions of the arterioles are not due to ischemia is shown by the absence of the lesions from the severely ischemic kidneys of the dogs and their presence in organs in which there is no preexistent ischemia. In the dogs, at least, the combination of hypertension and severe disturbance of renal function, with consequent accumulation of chemical substances in the blood, is at least a necessary condition for the manifestation of the arteriolar necrosis and associated hemorrhages in various organs. Since the hypertension is not present within the intrarenal blood vessels of the animals with the main renal arteries, or the aorta above the origin of the renal arteries, constricted, the lesion does not manifest itself there. The same explanation (absence of local hypertension) probably applies to the absence of the lesion in the pulmonary arterioles of man as well as of animals. What the nature of the chemical substance or substances is that plays a part in the production of these lesions is not elucidated by these investigations on experimental hypertension that have been carried out so far but they do show that hypertension, severe disturbance of renal excretory function, and generalized degenerative changes, including severe hyalinization and necrosis, of the arterioles, all indistinguishable from those found in the malignant phase of hypertension in man, can be induced experimentally by severe reduction of the blood supply to the kidneys.

The results of all the investigations that have dealt with the pathogenesis of the benign phase of experimental hypertension due to constriction of the main renal arteries apply equally well to the malignant phase. The only experimental condition that determines the type of hypertension is the degree of constriction of the main renal arteries.

One obvious surgical therapeutic procedure which suggests itself as the result of this work is the possible improvement of blood supply to the functioning components of the kidney by increasing the accessory circulation. In the animals with experimental hypertension induced by renal ischemia, whenever there is a return of the blood pressure to a lower level, it is due to inadequate initial clamping of the renal arteries or to the development of effective accessory circulation by way of ureteral and capsular vessels, which become very prominent. If, before constricting the renal artery, the kidney is decapsulated and adipose tissue or muscle is attached to the denuded cortical surface, the accessory circulation becomes very prominent and interferes with the development of

pronounced elevation of blood pressure. Since in the animals the constriction is only of the main renal artery, such accessory circulation can be of functional significance. The fact that animals have survived several years the complete closure of both main renal arteries,[84] when effected gradually by increasing the constriction at intervals, is proof that such accessory circulation can be functionally highly effective. Unfortunately, in human essential hypertension, the vascular disease most frequently involves also the preglomerular arterioles, so that collateral communication with the larger vessels would not improve circulation to glomeruli. Whether improvement of blood supply to some glomeruli, to tubules and interstitial tissue would occur and whether it would be effective in lowering blood pressure in human essential hypertension cannot be determined without trying. Although the author has hesitated to recommend it, yet there is probably more justification on an experimental basis for making this test than there has been for some of the surgical procedures that have already been practiced. The cases in which the production of accessory circulation would be most effective would be those in which the hypertension is due to sclerosis of the main renal arteries alone[41] or their very large branches. The difficulty of making such a diagnosis is obvious, so that unless the method could be applied to essential hypertension associated with renal arteriolar sclerosis the procedure would be of greatly restricted value.

An interesting practical application of this work, which centers upon the renal origin of so-called essential hypertension, has been the finding in children[217] and adults[218] of hypertension associated with unilateral pyelonephritis and vascular disease, and the prompt return of the blood pressure to normal after excision of the diseased kidney.[217,218] Until 1930, according to Bell and Pedersen[219] hypertension associated even with bilateral pyelonephritis had not been reported. Since then several authors[220-223] have reported this occurrence in some cases and from the meager studies of the kidneys in these cases it becomes probable that the hypertension associated with unilateral or bilateral pyelonephritis in children and adults occurs only in those cases in which there is associated vascular sclerosis or in which the inflammatory disease produces the same effects on renal circulation as does vascular disease. In cases of unilateral arteriolar nephrosclerosis with hypertension, which have been reported by Moritz and Oldt,[35] if the diagnosis could be made in life, removal of the diseased kidney might result in a return of the

blood pressure to normal, as in the cases of unilateral pyelonephritis.* Unfortunately, unless the production of accessory circulation would be effective, nothing but transplantation of a normal kidney or kidneys, with removal of both diseased kidneys, could be expected to relieve the hypertension and prove the renal origin of the disease in cases of human hypertension associated with bilateral pyelonephritis or arteriolar sclerosis of the kidneys. Whether this can ever be accomplished in man, as it can in animals, is for the future to disclose.

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* From the James Buchanan Brady Urological Institute and Department of Medicine of Johns Hopkins Hospital there have just been reported[228,229] two cases of hypertension associated with unilateral renal vascular disease in which the removal of the diseased kidney resulted in a prompt return of the blood pressure to normal. A similar result has been obtained in a third unreported case (Personal Communication, Professor Hugh Young).

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